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A New Approach for Asymmetric Synthesis of (-)-Umbelactone

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Abstract: A concise and efficient total synthesis of (-)-umbelactone **1**, an occurring γ-hydroxymethyl-α, β-butenolide from *Memycelon umbelatum* Burm, is described. The synthesis features the use of a ring closing metathesis strategy.

Keywords: (-)-Umbelactone, catalysis, metathesis, ruthenium.

α, β-Butenolide is of biological relevance and is presented in a variety of physiologically active compounds[1]. (*R*)-(+)-Umbelactone is an example of a naturally occurring γ-hydroxymethyl-α, β-butenolide, which was isolated from *Memycelon umbelatum* Brum[2]. This natural product is of particular interest since it showed activity against Ranikhe disease virus and spasmolytic and antiamphetamine activity[3]. Accordingly, considerable efforts toward its synthesis have been made by several groups, culminating in the first total synthesis reported by Ukachukwu[4a], confirming the absolute stereochemical configuration proposed by Front[4b], elegant synthesis by Handa[4d] and Fujisawa[4c] underline the importance and appeal of this natural product. Study on biological and biochemical properties of the enantiomer of (*S*)-(-)-umbelactone **1** has not been reported. In the interest of fully evaluating the biological properties of umbelactone it is desirable to obtain adequate supplies of both (*R*)-(+)-umbelactone[4] and its enantiomer, (*S*)-(-)-umbelactone **1**[4b]. Front described the synthesis of this enantiomer by using D-ribonolactone[4b]. In this paper we reported a new asymmetric synthesis of (*S*)-(-)-umbelactone **1** in six steps and 28% overall yield with the ring-closing olefin metathesis (RCM) as the key step (**Scheme 1**).

An important component of our strategy involved the use of the ring-closing olefin metathesis reaction to build lactone. Due to its tolerance to many different functional groups, efficiency and mild conditions, the method has allowed for more efficient access to (-)-umbelactone **1** and more flexible access to α, β-butenolide analogues.

In our approach, we started from intermediate **2 (Scheme 1**), which were synthesized from D-mannitol in four steps[6]. Compound **2** is a valuable, readily available chiral substrate susceptible to various transformations, which may be useful for stereocontrolled synthesis. Compound **2** was deprotected to afford alcohol **3** by treatment with concen-

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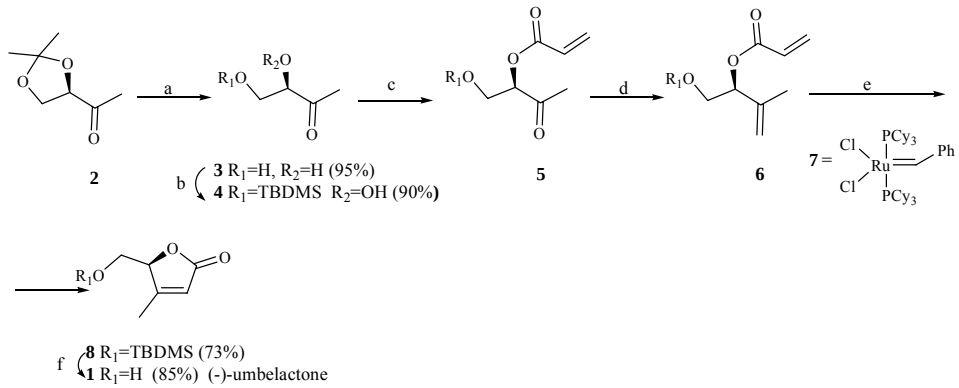
Scheme 1 Total synthesis of (-)-umbelactone by RCM



Reagents and conditions: (a) concentrated HCl/ethanol, rt, 2 h; (b) TBDMSCl, DMAP, Et_3N, DMF, 0 to 25 ^{0}C, overnight; (c) H_2C=CHCOCl, Et_3N, THF, reflux, 6 h, 76%; (d) [$Ph_3P^+CH_3Br^-$/ BuLi], HMPA/THF, 0 to 25 ^{0}C, overnight, 70%; (e) Grubbs′ catalyst **7** (5 mol-%), cat. Ti(*i*PrO)$_4$, CH_2Cl_2, 35 ^{0}C; (f) AcOH: H_2O: THF(3:1:1 v/v), rt, 8 h.

trated HCl in ethanol at room temperature for 2 h. Selective silylation of **3** gave monoprotected diol **4**, with TBDMSCl in the present of Et_3N, DMAP in DMF[7]. Compound **4** with acrylic chloride afforded the ester **5**[8]. The Wittig reaction was performed by treatment of **5** with $Ph_3P^+CH_3Br^-$, BuLi, and HMPA/THF. Ring closing metathesis (RCM) using Grubbs′ catalyst **7** afforded the compound **8** in the present of catalytic amounts of Ti(*i*PrO)$_4$. Following the work of Fűrstner *et al.* Ti(*i*PrO)$_4$ was used to avoid interruption of the catalytic cycle by chelation of the substrate carbonyl to the metal[10]. The TBDMS protecting group was cleanly removed under mild, acidic conditions [AcOH: H_2O: THF (3:1:1 v/v)], and the resulting lactone **1**[11]has showed identical spectral data with those of (-)-umbelactone reported.

In summary, we have a total synthesis of (S)-(-)-umbelactone **1** in six synthetic operations with an overall yield of 28%. This approach seems to be flexible enough for the synthesis of various analogues of this α, β-butenolide on the basis of its wide application and mild reaction conditions. Finally, it is worth mentioning that the macrocylization by C-C coupling employing the newly developed binary RCM catalyst system is significantly more productive than the well established macrolactonization strategies previously employed[10]. The biology of (-)-umbelactone **1** will be studied and reported at a later date.

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References and Notes

1. (a) Y. S. Rao, *Chem. Rev.,* **1977**, *76*, 625. (b) A. A. Avetisysan, M. T. Dangyan, *Russ. Chem. Rev.,* **1977**, *46*, 643. (c) R. C. Larock, B. Riefling, C. A. Fellows, *J. Org. Chem.,* **1978**, *43*, 131.
2. S. K. Agarwal, R. P. Rastogi, *Phytochemistry,* **1978**. *17*, 1633.
3. M. L. Dhar, M. M. Dhar, B. N. Dhawan, *et al*., *Indian J. Exp. Biol.,* **1968**, *6*, 241.
4. (a) D. Caine, A. S. Frobese, V. C. Ukachukwu, *J. Org. Chem.,* **1983**, *48*, 740. (b) R. M. Ortuño, J. Bigorra, J. Front, *Tetrahedron,* **1987**, *43*, 2199. (c) T. Sato, Y. Okumura, J. Itai, T. Fujisawa, *Chem. Lett.,* **1988**, 1537. (d) C. L Gibson, S. Handa, *Tetrahedron: Asymmetry*, **1996**, *7*, 1281.
5. Reviews: (a) M. Schuster, S. Blechert, *Angew. Chem., Int. Ed. Engl.,* **1997**, *36*, 2036. *Angew. Chem.,* **1997**, *109*, 2124. (b) S. K. Armstorng, *J. Chem. Soc, Perkin Trans. 1,* **1998**, 371. (c) R. J. Grubbs, S. Chang, *Tetrahedron,* **1998**, *54*, 4413.
6. J. urczak, S. Pikul, T. Bauer, *Tetrahedron.,* **1986**, *42*, 447.
7. (a) S. K. Chaudhary, O. Hernandez, *Tetrahedron Lett.,* **1979**, 99. (b) K. K. Ogilive, A. L. Shiftman, C. L. Penney, *Can. J. Chem.,* **1979,** *57*, 2230.
8. W. Herz, R, R. Juo, *J. Org. Chem.,* **1985**, *50*, 618.
9. (a) B. E. Maryanoff, A. B. Beitz, *Chem. Rev.,* **1989**, *89*, 863. (b) E. M. Suh, Y. Kishi, *J. Am. Chem. Soc.,* **1994**, *116*, 11205.
10. A. Fűrstner, K. Langemann, *J. Am. Chem. Soc.,* **1997**, *119*, 9130.
11. Spectral data: Compound **5** (76%): $[\alpha]_D^{20}$–3.6 (*c* 5.60, $CHCl_3$); IR (film): 1791, 1729, 1407, 1257, 1184, 1129, 838 cm^{-1}; EIMS (*m/z*): 245 (0.8, M-27), 215 (5.1, M-57), 55 (100); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 6.51 (d, 1 H, *J* = 17.1 Hz), 6.22 (dd, 1H, *J* = 17.1, 10.7 Hz), 5.93 (d, 1H, *J* = 10.7 Hz), 5.12 (t, 1H, *J* = 4.2 Hz), 3.91-4.08 (m, 2H), 2.22 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 204.6, 165.4, 132.0, 127.7, 79.5, 62.9, 27.6, 25.7, 18.2, -5.3, -5.6. Anal. Calcd. for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.88. Found: C, 57.26; H, 8.95. Compound **6** (70%): $[\alpha]_D^{20}$ –2.9 (*c* 1.60 $CHCl_3$); IR (film): 2955, 2932, 1731, 1467, 1406, 1260, 1191, 1133, 839 cm^{-1}; EIMS (*m/z*): 213 (0.3, M-27), 129 (100); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 6.54 (dd, 1H, *J* = 17.4 Hz, 1.8Hz), 6.15 (dd, 1H, *J* = 17.4 Hz, 10.7Hz), 5.83 (dd, 1H, *J* = 10.7 Hz, 1.8Hz), 5.29 (t, 1H, *J* = 6 Hz), 5.00 (s, 1H), 4.94 (s, 1H), 3.75 (d, 2H, *J* = 6 Hz), 1.77 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 165.4, 141.1, 130.7, 128.6, 113.3, 77.8, 64.1, 25.7, 19.2, 18.2, -5.4. Anal. Calcd. for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.20; H, 9.81. Compound **8** (73%): $[\alpha]_D^{20}$ –11.2 (*c* 1.8, $CHCl_3$) IR (film): 2955, 2931, 2858, 1761, 1649, 1468, 1311, 1256, 1133, 839 cm^{-1}; EIMS (*m/z*): 212 (0.9), 185 (M-57, 100); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 5.83 (m, 1H), 4.81 (m, 1H), 4.02 (d, 1H, *J* = 12.1Hz), 3.70 (d, 1H, *J* = 12.1Hz), 2.09 (s, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 173.4, 166.7, 117.8, 84.7, 61.7, 25.7, 18.1, 14.1, -5.6. Anal. Calcd. for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.55; H, 9.23. Compound **1** $[\alpha]_D^{20}$ -10.6 (*c* 1.0, $CHCl_3$); EIMS (*m/z*): 129 ($M+H^+$, 32), 41 (100). ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 5.87 (m, 1H), 4.90 (m, 1H), 4.07 (dd, 1H, *J* = 12.1, 4.2 Hz), 3.74 (dd, 1H, *J* = 12.1, 4.2 Hz), 2.56 (m, 1H), 2.10 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 173.4, 167.0, 117.4, 85.2, 60.6, 13.7. Anal. Calcd. for $C_6H_8O_3$: C, 56.25; H, 6.30. Found: C, 56.26; H, 6.36.

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